PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT-8217	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IT2004/000184	International filing date *(day/month/year)* 07.04.2004	Priority date *(day/month/year)* 24.04.2003
International Patent Classification (IPC) or national classification and IPC A61K47/48, A61K39/395, A61K31/4188, A61K51/00, A61P35/00		
Applicant SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUN... et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) ; containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.11.2004	22.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Ulbrecht, M Telephone No. +49 89 2399-7710

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IT2004/000184

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-17 received on 01.12.2004 with letter of 22.11.2004

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 3
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 2 (with respect to IA)

because:

☒ the said international application, or the said claims Nos. 2 (with respect to IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IT2004/000184

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,2,4-17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,2,4-17
Industrial applicability (IA)	Yes:	Claims	1,4-17
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re item I

Present claim 3 defines the first agent as being avidin. The second agent is not defined apart from its specifity and anticancer effect. The application as originally filed, however, only mentions the combined use of avidin as first agent together with biotin bearing the anticancer agent as second agent. As claim 3 does not have a basis in the application as originally filed it was not subject to the IPER.

Re item III.

Claim 2 relates to subject-matter considered by this Authority to be covered by the provisions of R. 67.1(iv) PCT. The wording of said claim is such that it has to be construed as referring to a method of treatment. Consequently, no opinion has been formulated with respect to the industrial applicability of the subject-matter of this claim (Art.34(4)(a)(i) PCT).

Re Item V.

1. The following documents are referred to in this communication:

D1 : EP 0 496 074 A (MINI-RICERCA SCIENT TECNOLOG) 29 July 1992 (1992-07-29)

D2 : PAGANELLI G ET AL: "PRE-TARGETED LOCOREGIONAL RADIOIMMUNOTHERAPY WITH 90Y-BIOTIN IN GLIOMA PATIENTS: PHASE I STUDY AND PRELIMINARY THERAPEUTIC RESULTS" CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS, LIEBERT, US, vol. 16, no. 3, 2001, pages 227-235

D3 : EP 0 251 494 A (UNIV LELAND STANFORD JUNIOR) 7 January 1988 (1988-01-07)

D4 : KNOX S J ET AL: "Phase II trial of yttrium-90-DOTA-biotin pretargeted by NR-LU-10 antibody/streptavidin in patients with metastatic colon cancer." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. FEB 2000, vol. 6, no. 2, February

2000 (2000-02), pages 406-414

D5 : BOERMAN OTTO C ET AL: "Pretargeted radioimmunotherapy of cancer: Progress step by step." JOURNAL OF NUCLEAR MEDICINE, vol. 44, no. 3, March 2003 (2003-03), pages 400-411

2. The subject-matter of claims 1, 2 and 4-17 is novel as none of the prior art documents discloses the combination of features suggested by the said claims (Art. 33(2) PCT).

3.1 The characterising features of claim 1 relate in fact to a method of treatment. Whereas the individual components of the medicament i.e. e.g. a biotinylated antibody specific for tumour-associated antigens, avidin and a conjugate of biotin with a radioisotope are already known from D2 (abstract; p. 228, c. 2, c. 1 - p. 230, c. 2, para. 1), the subject-matter of claim 1 is distinguished from D2 by the timing of the administration of the different components. In D2 all components are applied locoregionally after a tumour resection. According to claim 1 the said components are administered perioperatively which was construed as referring to the intraoperative administration of some of said components followed by the postoperative administration of the remaining components (cf. p. 3, para. 2 and p. 4, para. 4 of the description as well as V 5. herein below). However, this modification of the administration scheme is considered to fall within the routine modification of the method of D2, and, as it does not bring about any surprising technical effect is not considered to establish an inventive step (Art. 33(3) PCT).

3.2 D1 discloses a kit including a first container containing a biotinylated monoclonal antibody specific for tumour-associated antigens, a second container containing avidin, and a third container containing biotin conjugated to radioisotopes or cytotoxic agents and, preferably, a fourth container containing biotinylated albumin (c. 2, l. 21-32; and c. 7, l. 19-32). This kit is suitable for two-step therapy. The subject-matter of claim 15 differs from D1 in that the suggested kit consits of only the second and the third container of the kit according to D1. This, however, is any arbitrary selection of kit components which the skilled person would choose out of equally likely alternatives of kits providing the reagents for the method of D1. Thus, claim 15 lacks an inventive step over D1 (Art. 33(2) PCT).

3.3 The medicament according to claim 1 consists inter alia of a biotinylated tumour-specific antibody, avdidin and a conjugate of a radioisotope with biotin (cf. e.g. p. 4, para. 4 of the description). Such a medicament is used in a method of pretargeted radioimmunotherapy according to D2 (abstract; p. 228, c. 2, c. 1 - p. 230, c. 2, para. 1). Concomittantly with the said therapy the biodistribution of the said medicament is determined (p. 230, c. 2, para. 2 - p. 231, c. 2, para 1; Fig. 2). The subject-matter of claim 17 differs from D2 representing the closest prior art in that this biodistribution is determined pretherapeutically. However, this is a modification of the method of D2 falling within the scope of routine modification without producing any unforeseeable technical effect, and which therefore does not establish an inventive step. Hence, claim 17 is not considered inventive (Art. 33(3) PCT).

3.4 D3-D5 disclose methods of pretargeted radioimmunotherapy in which avidinated antibodies specific for tumour-associated antigens are applied first, followed by the application of biotin conjugated to an anticancer compound (D3: p. 2, l. 24 - p. 5, l. 20; D4: abstract, p. 407, c. 2, para. 3 - p. 409, c. 1, para. 1; D5: p. 403, c. 2, para. 2 - p. 405, c. 1, para. 1). In said methods the components of the kit according to claim 16 are used. Inclusion of the said components into a kit to provide the less skilled with the reagents necessary to perform the method of any of D2-D4 is a matter of routine and does not establish an inventive step. Hence, the subject-matter of claim 16 is not considered inventive (Art. 33(3) PCT).

3.5 The additional technical features suggested by claims 5-11 are also disclosed in D2 (supra) and, thus, do not establish an inventive step (Art. 33(3) PCT).

3.6 The additional features suggested by claims 2, 4 and 12-14 relate to further routine modifications of the method of D2 (cf. V 3.1) which do not result in any unforeseeable technical effect and which thus do not establish an inventive step (Art. 33(3) PCT).

4.1 For the assessment of the present claim 2 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of

a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4.2 The subject-matter of claims 1 and 4-17 appears to be industrial applicable (Art. 33(4) PCT).

5. The terms "two-step perioperative therapy" and "pretherapeutic" used in claims 1 and 17 are vague and unclear and leave the reader in doubt as to the technical features to which they refer thereby obscuring the definition of the subject-matter of said claims (Art. 6 PCT). The term "two-step perioperative therapy" was interpreted as referring to a first intraoperative and a second postoperative step of performing the pret-targeted radioimmunotherapy (cf. p. 3, para. 2 and p. 4, para. 4 of the description). The term "pretherapeutic" was interpreted as referring to the time period before the application of the conjugate of biotin with the radioisotope.

CLAIMS

1. Use of a first agent endowed with tumour tropism in combination with a second anticancer agent endowed with affinity for said first agent as active ingredients for the preparation of a medicament useful for the two-step perioperative therapy of solid tumours.

2. Use according to claim 1, in which said first agent is administered during an intraoperative step via the locoregenional route and said second agent is administered during a postoperative step via the systemic route.

3. Use according to any of the foregoing claims, in which said agent endowed with tumour tropism contains avidin.

4. Use according to any of the foregoing claims, in which said first agent is avidin and said second agent is a biotin compound bearing an anticancer agent.

5. Use according to any of the foregoing claims, in which said anticancer agent is selected from the group consisting of radioisotopes, chemotherapeutic agents, toxins and anticancer cells.

6. Use according to claim 5, in which said radioisotope is selected from the group consisting of Fe-52, Mn-52m, Co-55, Cu-64, Ga-67, Ga-68, Tc-99m, In-111, I-123, I-125, I-131, P-32, Sc-47, Cu-67, Y-90, Pd-109, Ag-111, I-131, Pm-149, Re-186, Re-188, At-211, Pb-212, Bi-212, and Lu-177.

7. Use according to claim 6, in which said radioisotope is Y-90 or Lu-177.

8. Use according to claim 4, in which the avidin and the biotin compound in said medicament are in separate containers.

9. Use according to one of the foregoing claims, in which said tumour is selected from the group consisting of breast, pancreas, lung, pleural, peritoneal, cervico-facial, brain and bladder tumours.

10. Use according to one of claims 3-9, in which said avidin is selected from the group consisting of avidin, streptavidin, their polymeric derivatives and their derivatives with polyethylene glycol..

11. Use according to one of the foregoing claims, in which said medicament is suitable for injectable administration.

12. Use according to claim 11, in which the container of said avidin is in the form of a syringe suitable for successive administrations of precise volumes.

13. Use according to claim 4, in which said avidin is contained in a separate container in a single dose.

14. Use according to claim 4, in which the container of said avidin is suitable for administration in the form of a spray.

15. Kit for two-step perioperative therapy, consisting of a set of separate containers, in which a first container contains an avidin compound, and a second container contains a biotin compound bearing an anticancer agent.

16. Kit according to claim 15, in which the first container contains an avidinated antibody specific for antigens associated with a tumour or a mixture of antibodies, and the second container contains a biotin compound bearing an anticancer agent.

17. Use of a first agent endowed with tumour tropism in combination with a second radiolabelled agent endowed with affinity for said first agent for the preparation of a diagnostic composition for the pretherapeutic biodistribution of the medicament according to claim 1.